II. REMARKS:

A. Status of the Claims

Claims 1-9 were originally filed with the case. Claim 1 was amended in response to an Official Action mailed January 18, 2002. Claims 1-9 were pending at the time of the present Action. No claims are amended, added or cancelled herein. Claims 1-9 remain pending.

B. The Claims are Enabled

The Action rejects claims 1-9 under § 112, first paragraph as lacking enablement. According to the Action, the specification is enabling for treating an angiogenesis-related disorder but does not provide enablement to prevent the same disorders. Claim 1 has been amended to clarify the subject matter of the invention as directed to treating angiogenesis-related disorders rather than preventing them. It is believed that the amendment to the claim renders the enablement rejection moot. Therefore, Applicants respectfully request that the enablement rejection be withdrawn.

C. The Claims are Definite

The Action further rejects claims 1-9 under § 112, second paragraph as being indefinite for failing to particularly point out the subject matter of the invention. Specifically, the Action states that the language "a method of ... preventing an angiogenesis-related disorder in a patient suffering from such a disorder" is confusing. In light of the amendment to claim 1 to delete the term "preventing," it is believed that the definiteness rejection is rendered moot. Therefore, Applicants respectfully request that the definiteness rejection be withdrawn.

D. The Claims are Patentable Over Hellberg in Combination with Daniel and Yamada

The Action rejects claims 1-8 as being unpatentable over Hellberg (U.S. Patent No. 6,342,524) in combination with Daniel and Yamada. Hellberg is said to disclose that nepafenac inhibits prostaglandin synthesis. Yamada and Daniel are said to teach the correlation between COX-2 inhibitors and angiogenesis. Therefore, the Action reasons that it would have been obvious that the claimed compounds would have angiogenesis inhibiting properties stemming from their COX-2 inhibiting properties. Applicants respectfully traverse.

Hellberg discusses the use of certain compounds to treat GLC1A glaucoma and does not discuss the treatment of angiogenesis-related disorders at all. Hellberg goes on beyond its first sentence to discuss the relationship of the GLC1A gene to the occurrence of glaucoma. The GLC1A gene encodes a 57 kD protein that is expressed in the trabecular meshwork (TM) (col. 2, lines 20-21). The expression of this protein is upregulated by glucocorticoids (col. 2, lines 23-25). The glucocorticoid induction of this TM protein has been suggested to be involved in the generation of glucocorticoid-induced ocular hypertension and glaucoma. (col. 2, lines 32-35). It is this effect, the increase in ocular hypertension caused by glucocorticoid induction of the GLC1A protein, that the '524 patent seeks to treat.

The '524 patent discusses the mechanism by which the glucocorticoid induction of the GLC1A protein causes an increase in ocular hypertension, or intraocular pressure (IOP). It states, in pertinent part:

> It is known that the trabecular meshwork cells have glucocorticoid receptors and that glucocorticoid binding with these receptors causes a change in trabecular meshwork cell gene expression. Known manifestations of this change include a reorganization of the cytoskeleton [ ] and increased deposition of the extracellular matrix material in trabecular meshwork cells. As a result, *the trabecular meshwork becomes "clogged" and unable to perform one of its most critical functions, that is, serving as a gateway for aqueous humor flow from the anterior chamber of the eye.*

> *When the aqueous humor flow out of the eye via the trabecular meshwork is diminished, the intraocular pressure of the eye rises.* If this state of elevated intraocular pressure (IOP) is maintained or frequently occurs, the optic nerve head can be damaged resulting in the loss of visual field.

(col. 3, lines 16-37, *citations omitted, emphasis added*). Hellberg's objective is to decrease the IOP in glaucoma patients suffering from an increased IOP due to glucocorticoid induction of the expression of the GLC1A. Hellberg does not discuss the administration of derivatives of 3-benzoylphenylacetic acid to treat angiogenesis-related disorders. In fact, Hellberg discusses the use of such compounds only in combination with a prostaglandin for the treatment of GLC1A glaucoma. Hellberg does not discuss the use of derivatives of 3-benzoylphenylacetic acid by themselves to treat angiogenesis-related disorders.

The purpose of the presence of non-steroidal cyclooxygenase inhibitors in the combinations of Hellberg is to prevent the expression of GLC1A and thereby prevent the development of ocular hypertension or increased IOP. (col. 5, lines 20-22). The prostaglandin in the compositions of Hellberg provides the "acute effect" for lowering IOP. The non-steroidal cyclooxygenase inhibitors, used in combination with the prostaglandins, are present to ameliorate the undesirable secondary side effects associated with prostaglandin therapy for the treatment of glaucoma, without significantly interfering with the desired IOP lowering. (col. 5, lines 28-35). Clearly, Hellberg's objective is to treat GLC1A glaucoma by lowering IOP, not to directly treat angiogenesis-related disorders. In fact, glaucoma is not considered an angiogenesis-related disorder.

It is well settled patent law that "obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art." *See In re Fine*, 837 F.2d 1071,

5 U.S.P.Q.2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 U.S.P.Q.2d 1941 (Fed. Cir. 1992); MPEP § 2143.01.

Furthermore, the fact that a reference or references can be combined or modified is not sufficient to establish obviousness. For example, the Federal Circuit held in *In re Mills*, 916 F.2d 680, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990), that the mere fact that combination or modification of a reference or references is possible does not establish obviousness of the resultant combination unless the prior art also suggests the desirability of the combination, *i.e.*, unless the prior art provides motivation to produce the resultant combination. *Mills*, 16 U.S.P.Q.2d at 1432; *see also* MPEP § 2143.01, page 2100-91.

The Action appears to be ignoring what Hellberg *fairly suggests* to one skilled in the art." *Bausch & Lomb*, 230 U.S.P.Q. at 419. As discussed above, Hellberg suggests to the skilled artisan that the administration of derivatives of 3-benzoylphenylacetic acid in combination with a prostaglandin will prevent the expression of GLC1A and thereby prevent the development of ocular hypertension or increased IOP. (col. 5, lines 20-22). The prostaglandin in the compositions of Hellberg provides the "acute effect" for lowering IOP. The non-steroidal cyclooxygenase inhibitors, used in combination with the prostaglandins, are present to ameliorate the undesirable secondary side effects associated with prostaglandin therapy for the treatment of glaucoma, without significantly interfering with the desired IOP lowering. (col. 5, lines 28-35). Clearly, Hellberg's objective is to treat GLC1A glaucoma by lowering IOP.

There is no suggestion or motivation within Hellberg to administer the compounds of the present invention by themselves for the sole purpose of treating angiogenesis-related disorders. As explained above, the focus of the invention of Hellberg is to lower IOP by administering a combination of compounds. The remainder of the description of the problem and the solution

provided in Hellberg focuses on the increase of ocular hypertension caused by glucocorticoid induction of the GLC1A protein. This is what Hellberg seeks to treat.

Neither Yamada nor Daniel discuss the compounds of the present invention at all. The references both appear to discuss COX-2 inhibition and its effects on angiogenesis, but neither mention amfenac, nepafenac or any ophthalmic angiogenic-related disorder other than corneal neovascularization. The present invention is the first to show that nepafenac and related compounds can be used to treat an angiogenesis-related disorder. Thus, Yamada and Daniel cannot render the claimed invention obvious, either alone or in combination.

In light of the foregoing arguments, Applicants respectfully request that the rejected based on Hellberg in combination with Daniel and Yamada be withdrawn.

E. The Claims Are Patentable over Hellberg in view of Daniel or Yamada in further view of Liu

The Action next rejects claim 9 as being unpatentable over Hellberg in view of Daniel or Yamada as applied to claims 1-8 in further view of Liu. Liu is said to disclose that COX-2 inhibitors modulate prostate cancer angiogenesis. The Action notes that the publication date of Liu is 1999 and that the Applicants have submitted a declaration establishing a reduction to practice prior to October 21, 1999. The Action indicates that Liu might have been published prior to the date established in the declaration and that the Examiner is in the process of obtaining the exact date of availability for Liu. Applicants believe that they were in possession of the subject matter of the invention well before the October 21, 1999 date listed for Liu and will submit a declaration to that effect if deemed necessary. It is believed that Liu will not qualify as prior art even if the actual availability is slightly prior to the October 21, 1999 date listed on the publication. Therefore, it is submitted that the obviousness rejection based on Hellberg in view

of Daniel or Yamada in further view of Liu is overcome. Applicants respectfully request that the rejection be withdrawn.

F. The Double Patenting Rejections Will be Overcome with Terminal Disclaimers When Appropriate

Next, the Action provisionally rejects claims 1-9 under the judicially created doctrine of obviousness-type double patenting doctrine as being unpatentable over copending Application Nos. 10/344,881 and 10/417,466. The Action points out that these rejections are provisional, in that the copending applications have not yet been allowed. Applicants will file terminal disclaimers to overcome these provisional rejections upon a notice of allowability of the presently pending claims.

G. Conclusion

This is submitted to be a complete response to the outstanding Action. Based on the foregoing arguments, the claims are believed to be in condition for allowance; a notice of allowability is therefore respectfully requested.

The Examiner is invited to contact the undersigned attorney at (817) 551-4321 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

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